

enabled. The Examiner has asserted that the quantity of experimentation needed to practice the full scope of the instant Invention is great, and there is little, if any reasonable expectation of success. The Examiner also believes that: (a) the amount of guidance provided in the instant Application is limited; (b) that only one example is given; (c) that the instant Invention is inherently unpredictable due to the nature of the instant Invention i.e., matters of physiology and chemistry; and (d) that the relative skill of those in the art that is most closely associated with the instant Invention is high, i.e., on par with those holding a Ph.D. in biochemistry.

Furthermore, the Examiner has admitted that the pending Claims contain sufficient breadth of scope so as to encompass amplification of one or a plurality of target sequences in a common reaction where a plurality of primers are present, and wherein not all primers in the reaction are permitted to prime an extension reaction, due to a mismatch on the 3'-terminus. It is the Examiner's belief however, that in order for one of skill in the art to practice the full scope of the claimed Invention, the public would have to finely tune the reaction conditions to where a plurality of primers can be used, and wherein at least one of the primers will have a mismatch with the target sequence on the 3' terminus. The Examiner has also asserted that simultaneously, the mismatch primer must not also effectively anneal to non-target sequences so as to result in the amplification of non-target sequences. In the Examiner's opinion, such fine tuning of reaction conditions is imperative to practicing the claimed Invention. The Examiner also believes that the pending Claims have sufficient breadth of scope to encompass virtually any reaction condition. Hence, it is the Examiner's position that the instant Specification does not enable the Claims in their present form.

Applicant respectfully traverses this rejection. As explained above, the Examiner has

asserted that it would take “several man years” of undue experimentation in order for one of ordinary skill in the art to practice the instant Invention. The Examiner then went through a variety of contortions in attempting to demonstrate he had considered all of the factors set forth in MPEP §2164.01(a) in making this rejection. However, it is respectfully submitted that the Examiner has fallen short of his burden, and this rejection should be withdrawn. Initially, the Examiner asserted that that the amount of direction or guidance provided in the instant Specification is limited. However, it is respectfully submitted that sufficient guidance is provided throughout the instant Specification regarding the practice of the instant Invention. In particular, a large amount of information regarding solvents (page 62, lines 11-17); pH ranges and buffers (page 62, lines 18-21, page 63, lines 1-13); temperatures (page 63, lines 14-21 and page 64, lines 1-3); the number of PCR cycles; the time for the reaction; and the concentration of various reagents, materials used, e.g., primers, polynucleotides, nucleosides, etc. (page 64 through to page 67) for practicing the instant Invention are disclosed. Moreover, disclosed in the instant Specification is a specific example of the Invention. Consequently, in light of the instant disclosure, one of ordinary skill in the art need only perform some routine laboratory techniques in order to practice the instant Invention. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is *undue*. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Since routine laboratory techniques and experiments are not considered to be undue, it is respectfully submitted that sufficient information is disclosed in the instant Application to permit a skilled artisan to practice the instant Invention.

Furthermore, the Examiner’s assertion that only one working example is provided in the

instant Specification is not relevant to the assertion that the pending Claims are not enabled. Indeed, MPEP §2164.02 states that the example need only be “prophetic.” Furthermore, it has been judicially held that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). For reasons set forth above, the instant disclosure readily provides a skilled artisan sufficient information to practice the instant Invention without the performance of undue experimentation.

Other assertions the Examiner made in attempting to support his position that undue experimentation is required to practice the instant Invention are (1) the inherent unpredictability of physiology and chemistry, (2) that the relative skill of those in the art most closely associated with the claimed Invention is high, and (3) that the state of the prior art is not developed sufficiently to permit a skilled artisan to practice the instant Invention without performing undue experimentation. It is respectfully submitted however, that these assertions also lack merit. For example, the state of the art at the time the instant Application was filed readily provides enablement for the pending Claims. Pages 7-10 of the instant Application describe numerous pieces of prior art that were available at the time of filing, that are relevant to the instant Invention. Particular examples include, but certainly are not limited to WO 94/04706 (Kievits *et al.*), who teach adding a control sequence to a PCR reaction; Gilliland *et al.* (PNAS 87:27525-2729 (1990)), who disclose the use of competitive polymerase chain reaction; Teleenti *et al.* (J. Virol. Methods 39:259-268 (1992), who describe a competitive polymerase chain reaction using an internal standard; and U.S. Patent 5,043,272, which describes the amplification of nucleic acid

sequences using oligonucleotides of random sequence as primers. Indeed, Claims 1 and 2 have a “Jepson” type format (37 CFR 1.75(e)). Thus, elements of the instant Invention set forth in the preamble of these Claims "...are impliedly admitted to be old in the art...." *In re Ehrreich*, 590 F.2d 902, 909-910 200 USPQ 504, 510 (CCPA 1979). Hence, the state of the prior art readily permits one of ordinary skill in the art to practice the instant Invention.

Moreover, it is respectfully submitted the Examiner has failed support his assertion that the skill of one of ordinary skill in the art needed to practice the instant Invention is high, “on par with those that hold a Ph.D. in biochemistry.” It is well established that the polymerase chain reaction, which is highly relevant to the practice of the instant Invention, as well as the synthesis of polynucleotides and primers having a specific sequence, are taught in *undergraduate* biochemistry and biochemistry laboratory courses. Thus, even artisans having on a bachelors degree in this field inherently possess a working knowledge of techniques that are highly relevant to the practice of the instant Invention. Consequently, it is unreasonable for the Examiner to assert that “one of ordinary skill in the art” should possess a high level of skill as described by the Examiner.

With respect to the Examiner’s assertion that the nature of the invention is inherently unpredictable, MPEP §2164.05(a) makes clear that the nature of the invention is merely the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. For reasons set forth above: (1) the state of the prior art is sufficient for one of ordinary skill in the art to practice the instant Invention; (2) the instant disclosure provides sufficient information to permit a skilled artisan to practice the instant Invention; (3) the required level of skill needed by one of ordinary skill in the art to practice the invention is not high as defined by the

Examiner; and (4) the number of examples set forth in a disclosure is not necessarily relevant to the enablement of that disclosure. Hence, it is respectfully submitted that Examiner has failed to meet his burden regarding these three prongs of the criteria for evaluating whether undue experimentation is required to practice the instant Invention.

It is also respectfully submitted the Examiner has failed to show that the breadth of scope of the claims is not enabled. As explained above, the instant Application discloses sufficient information regarding temperature, number of cycles, pH conditions, concentration of reagents (including polynucleotides), etc. to enable a skilled artisan to practice the instant Invention without the performance of undue experimentation. Hence, the instant Claims are clearly enabled.

Finally, Applicant respectfully reminds the Examiner that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to **back up** assertions of its own with **acceptable** evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added)." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). In attempting to show that a large amount of undue experimentation is required in order to practice the instant Invention ("man-years"), the Examiner made broad general assertions, e.g.:

1. the amount of guidance provided is limited;
2. the claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable; and

3. the relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

However, for reasons set forth above, the Examiner has failed to back up these assertions with acceptable evidence. Hence, for the foregoing reasons, it is respectfully submitted the practice of the instant Invention does not require the performance of undue experimentation, and this rejection should be withdrawn.

Furthermore, Claims 53-57 have been rejected under 35 U.S.C. 112, first paragraph, as not being enabled. The Examiner has admitted that, as presently worded, Claims 53-57 have sufficient breadth of scope so as to encompass primers that will hybridize to any and all possible target sequences, whether known or unknown. However, the Examiner believes that the instant Specification does not reasonably suggest that Applicant was in possession of any and all possible primer combinations as presently claimed. Hence, it is the Examiner's position that the instant Specification does not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicant respectfully traverses this rejection. Claim 53 has been amended to be directed towards, *inter alia*, a kit for amplifying a ***target sequence contained within a target polynucleotide***. It is respectfully submitted that in order to be a "target" sequence of a "target" polynucleotide, then a skilled artisan must know the nucleotide sequence of the target polynucleotide. From this information, primers and the control polynucleotide can readily be prepared using routine laboratory techniques. Thus, this rejection should be withdrawn.

***The Invention is Definite***

Claims 4-6, 1-13, 27-29, 41-43, and 53-57 have been rejected under 35 U.S.C. §112,

second paragraph as being indefinite. The Examiner has asserted the term “substantially” recited in Claims 4, 11, 27, 41 and 53 is a relative term that renders the Claims indefinite. In particular, the Examiner believes that “substantially” is not defined by the Claims, and the instant Specification does not provide a standard for ascertaining the requisite degree. Thus, it is the Examiner’s opinion that one of ordinary skill in the art would not reasonably be apprised of the scope of the instant Invention.

Applicant respectfully traverses this rejection. It is well established that terms of approximation, e.g. “substantially,” are routinely used by patent practitioners in drafting claims. Moreover, the courts have sanctioned the use of such terms. For example, in *Seattle Box Co. v. Industrial Crating and Packing*, 731 F.2d, 829 (Fed. Cir. 1984), the court explained:

Definiteness problems often arise when words of degree are used in a claim. That some claim language may not be precise, however, does not automatically render a claim invalid. When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree. The trial court must decide, that is, whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification.

It is respectfully submitted that a standard for measuring the degree is provided in the pending Claims. For example, Claim 4 states, *inter alia*, that the modified oligonucleotide primer is substantially the same as the oligonucleotide primer “***...but contains a chemical modification at its 3'-end that prevents degradation, by said 3' to 5' exonuclease, of said 1 to 10 nucleotides*** (emphasis added).” This clause clearly provides the standard one of ordinary skill in the art would use to determine the meaning of the term “substantially,” i.e., the same as the oligonucleotide primer *except* for the 3' end modification. Similarly, qualifying clauses in

Claims 11, 27, 41 and 53 provide standards for determining the meaning of the term "substantially" recited in those Claims. Hence, it is respectfully submitted the term "substantially" recited in the pending Claims is readily clear and understandable to a skilled artisan, and this rejection should be withdrawn.

***Fees***

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

**CONCLUSION**

Applicant respectfully requests entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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**Version With Markings To Show Changes Made**

53. (Twice Amended) A kit for amplifying a target sequence contained within a target polynucleotide, comprising in packaged combination:

- (f) an oligonucleotide primer that can hybridize to a primer binding site of the target polynucleotide,
- (g) a control polynucleotide having a sequence to which said oligonucleotide primer hybridizes except for 1-10 nucleotides at the 3'-end [3-end] of said oligonucleotide primer,
- (h) a modified oligonucleotide primer that is substantially identical to said oligonucleotide primer except for a chemical modification at its 3'-end that prevents degradation, by a 3' to 5' exonuclease, of said 1 to 10 nucleotides,
- (i) nucleoside triphosphates, and
- (j) a polymerase having 3' to 5' exonuclease activity.